REMARKS

A. Status of the Claims

Claim 1 was pending at the issuance of the instant Office Action. The rejections set forth in the Office Action are traversed by argument below.

B. Claim 1 is not obvious over Fridovich et al. in view of Kato et al.

The Action rejects claim 1 under 35 U.S.C. § 103(a) as being unpatentable over Fridovich *et al.* (US 2002/0042407) in view of Kato *et al.* (US 5,665,769). The Action points out that Fridovich teaches the use of a compound of Formula I (shown in the Office Action on page 3) for treating diabetes mellitus I or II, macular degeneration, or glaucoma, but fails to teach the use of the compound for treating diabetic retinopathy. The Action proceeds to cite Kato *et al.* to point out that diabetic retinopathy and macular degeneration are both retinal disorders, that diabetic retinopathy is a complication of diabetes. Thus the Action concludes that one skilled in the art would have been motivated to use the compound taught by Fridovich to treat diabetic retinopathy, because Fridovich taught the compound was useful for treating diabetes, of which diabetic retinopathy is a complication, and macular degeneration, which is a retinal disorder. Applicants respectfully disagree.

The Action's reasoning to support this rejection relies on two points: (1) diabetic retinopathy is a complication of diabetes; and (2) diabetic retinopathy and macular degeneration are both retinal disorders. Applicants respectfully point out that teaching the use of a compound to treat a particular disease does not make it obvious to use that same compound to directly treat a particular complication of that disease, because it is possible that the disease may mostly provide the initial stimulus for the complication, but not be as involved in the propagation. A compound that treats diabetes, which is associated with the body's inability to produce sufficient amounts of insulin or respond to physiological concentrations of insulin, would not necessarily be considered useful to treat a disease of the

eye, such as diabetic retinopathy, which is a disease characterized by retinal neovascularization, retinal edema due to leaky retinal blood vessels, and dysfunction of the retinal ganglion cell (RGC) layer in the eye. Similarly, use of a compound that can treat macular degeneration to treat diabetic retinopathy would not necessarily be obvious simply because both are disorders of the retina. Diabetic retinopathy is a disease characterized by, not only neovascularization, but also significant dysfunction of the retinal ganglion layer as discussed above. Macular degeneration as described in Kato *et al.* (col. 6, line 40-41) is a distinct disease not involving the retinal ganglion cell layer, and it follows a well-described pathological sequence. The dry form of age-related macular degeneration (AMD), for example, is associated with deposition of fluorescent bodies called drusen between the retinal pigmented epithelium (RPE) and Bruch's membrane, thickening of Bruch's membrane that prevents nutrient-waste product exchange with the choroidal capillaries, loss of RPE cells due to sustained oxidative stress and inflammation, and dropout of photoreceptors. This dropout of photoreceptors is concentrated in the macular region and is termed geographic atrophy. Dry AMD frequently progresses to wet AMD, which is associated with elevated intra-retinal concentration of vascular endothelial growth factor leading to retinal neovascularization. Many of these blood vessels leak fluid, leading to retinal edema. Consequently, Applicants submit that the combination of Fridovich and Kato does not render claim 1 obvious, and respectfully request that this ground of rejection be withdrawn.

C. Claim 1 is not obvious over Fridovich et al. in view of Kato et al.

The Action rejects claim 1 under 35 U.S.C. § 103(a) as being unpatentable over Fridovich *et al.* (WO 99/23097) in view of Kato *et al.* (US 5,665,769). The Action points out that Fridovich teaches the use of a compound of Formula I (shown in the Office Action on page 3) for treating type I and type II diabetes and edema, but fails to teach the use of the compound for treating diabetic retinopathy. The Action proceeds to cite Kato *et al.* to point out that diabetic retinopathy and retinal edema are both retinal disorders, that diabetic retinopathy is a complication of diabetes. Thus the Action concludes that one skilled in the

art would have been motivated to use the compound taught by Fridovich to treat diabetic retinopathy, because Fridovich taught the compound was useful for treating diabetes, of which diabetic retinopathy is a complication, and because retinal edema is a retinal disorder. Applicants respectfully traverse.

Again, the Action's reasoning to support this rejection relies on two points: (1) diabetic retinopathy is a complication of diabetes; and (2) diabetic retinopathy and retinal edema are both retinal disorders. With respect to the first point, as discussed above, the use of a compound to treat a particular disease does not make it obvious to use the same compound to directly treat a particular complication of that disease. A compound that treats diabetes would not necessarily be considered useful to treat a disease of the eye, such as diabetic retinopathy. With respect to the second point, Fridovich does not specifically teach or suggest that *retinal* edema or any other eye disorders can be treated with the compound of Formula I. Therefore, one of skill in the art would not have been motivated to rely of Kato *et al.* for any reason with respect to the use of the compound of Formula I in Fridovich for treating an eye disorder such as diabetic retinopathy, because Fridovich does not suggest or teach that the compound can used in the eye for any purpose. Consequently, the claims are not obvious in view of Fridovich and Kato. Applicants, therefore, respectfully request that this ground of rejection be withdrawn.

D. Claim 1 is not obvious over Piganelli et al. in view of Kato et al.

The Action rejects claim 1 under 35 U.S.C. § 103(a) as being unpatentable over Piganelli *et al.* (US 2003/0032634) in view of Kato *et al.* (US 5,665,769). The Action points out that Piganelli teaches the use of a compound of Formula I (shown in the Office Action on page 3) for treating diabetes and that low molecular weight antioxidants can treat diabetes-specific microvascular disease of the retina. The Action also points out that Piganelli fails to teach the use of the compound for treating diabetic retinopathy. The Action proceeds to cite Kato *et al.* to point out that diabetic retinopathy is a complication of diabetes and is one of the diabetic microangiopathies. Thus the Action concludes that one skilled in the art would have

been motivated to use the compound taught by Piganelli to treat diabetic retinopathy, because Piganelli taught the compound was useful for treating diabetes-specific microvascular disease of the retina, and because diabetic retinopathy is a retinal disease associated with diabetes. Applicants respectfully disagree.

Diabetic retinopathy is associated not only with retinal microvascular dysfunction but also with dysfunction of the retinal ganglion cell (RGC) layer. Abnormalities in RGC function are frequently observed in diabetes patients before any noticeable vascular-related diabetic retinopathy symptoms (see, for example, Antonetti, *et al.*, *Diabetes* **2006**, *55*, 2401-2411, a copy of which is provided in Exhibit A). It is possible that the increase in vascular endothelial growth factor (VEGF) levels in the vitreous of most diabetic retinopathy patients may be an attempt by the dying RGCs to rescue themselves using the well-described neurotrophic properties of VEGF, and not only an attempt by the body to improvement blood perfusion of a hypoxic retina. Furthermore, diabetic microangiopathies and retinal microvascular dysfunction are not necessarily associated with RGC dysfunction. One of skill in the art would not necessarily find it obvious to use a compound to treat a disorder associated with RGC dysfunction simply because the compound was useful for treating other retinal disorders and complications of diabetes, none of which were associated with RGC activity. Consequently, there is nothing in Piganelli or Kato that would teach, suggest, or motivate one of skill in the art to use the Piganelli compound to treat diabetic retinopathy. Therefore, Claim 1 is not obvious in view of Piganelli and Kato.

Applicants, therefore, respectfully request that this ground of rejection be withdrawn.

E. Conclusion

This is submitted to be a complete response to the outstanding Action. Based on the foregoing arguments, the claims are believed to be in condition for allowance; a notice of allowability is therefore respectfully requested.

The Examiner is invited to contact the undersigned attorney at (817) 615-5330 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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